WHO Expert Committee on Tuberculosis

Ninth Report

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WHO EXPERT COMMITTEE ON TUBERCULOSIS

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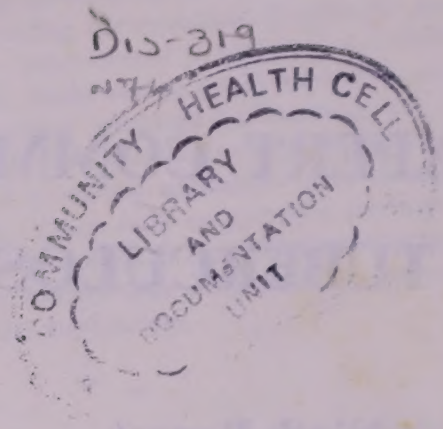

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Geneva, 11–20 December 1973

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WHO EXPERT COMMITTEE ON TUBERCULOSIS

Ninth Report

The WHO Expert Committee on Tuberculosis met in Geneva from 11 to 20 December 1973. The meeting was opened by Dr M. Takabe, Director, Division of Communicable Diseases, on behalf of the Director-General. In welcoming the members of the Committee, he said that tuberculosis remains a major health problem in all the developing countries. In some areas of Africa, Asia, and Oceania the reported annual incidence of pulmonary tuberculosis is 200–350 cases per 100 000 inhabitants and the prevalence is usually at least twice as high. The number of infectious cases of tuberculosis in the world at present is estimated to be in the range of 15–20 million.

Tuberculosis also remains a problem in many technically advanced countries : in countries where it is considered rare, it often causes more deaths than all other notifiable infectious diseases combined.

The Committee was asked to :

(1) review critically the validity of the recommendations contained in the eighth report of the Expert Committee,[1] in the light of scientific evidence that had subsequently become available ;

(2) make recommendations that could be acted upon and that would guide the Organization in giving advice and assistance to country health programming in the field of tuberculosis control ;

(3) propose ways in which physicians and other health workers could be motivated, oriented, educated, and trained for the tasks they will have to face in the future in connexion with the tuberculosis problem ;

(4) indicate areas of research to which priority should be given.

1. INTRODUCTION

The Committee reviewed the tuberculosis situation in the world and emphasized that tuberculosis still ranks among the major health problems, especially in the developing countries where over two-thirds of the world's

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 290.

population are struggling for socioeconomic development with resources that represent little more than one-tenth of the world's annual gross product. Moreover, in many technically advanced countries, tuberculosis and its sequelae still remain more important causes of death than all the other notifiable infectious diseases combined. The annual case load in the older age groups will remain considerable for many years to come.

The Committee noted that the eighth report had offered, for the first time, the concept of a comprehensive tuberculosis control programme on a countrywide scale. This concept was in many respects a challenge to the medical profession, both in technically advanced and in developing countries and its principles are still valid.

The implementation of the new approach to tuberculosis control has, however, encountered many problems. Shortages of financial, material, and physical resources and a shortage and maldistribution of trained manpower are aggravated by a lack of managerial skill. The health infrastructures of many countries, therefore, have deficiencies that remain uncorrected. These often lead to an increasing feeling of dissatisfaction because of the inability to apply, on an adequate scale, the potent weapons against tuberculosis. In some countries, a major constraint has been a reluctance to change traditional and outmoded orientations. Determined leadership is needed to effect the necessary changes and to apply more effectively the potent measures available for tuberculosis control.

The Committee noted that, in spite of difficulties, a number of countries have successfully implemented comprehensive national tuberculosis control programmes, or have adopted some of the main policies recommended in the eighth report. In consequence, in many countries, tuberculosis has changed from being a clinical specialty and has become a widely applied community health activity.

The Committee decided to focus its attention mainly on the control of pulmonary tuberculosis, and in particular its control in the very large number of countries where tuberculosis remains a serious public health problem and where, in order to achieve an impact on the problem, it is especially necessary to make the best possible use of limited resources.

The Committee emphasized particularly the need to formulate national tuberculosis programmes based on sound principles. Such programmes form the main feature of this report because their introduction is vital to worldwide control and the elimination of tuberculosis as a public health problem.

2. EPIDEMIOLOGY

The main aim of modern epidemiology is to provide data to make it possible to set clear programme priorities based on the dynamics and interactions of epidemiological events and on the impact of tuberculosis control measures on the trend of the disease.

The Committee recognized that there are many defects in most current systems of reporting and recording and stressed the importance of well planned and standardized approaches to all aspects of data processing, from collection to analysis and presentation. International epidemiological information, fed by a steady flow of comparable data coming from many parts of the world, is also of value to the individual countries contributing to such international efforts.

2.1 Epidemiological indices

Since the introduction of effective chemotherapy, mortality data have very little value as an index of the magnitude of the tuberculosis problem. However, a high mortality rate is a clear indication of an inadequate programme.

Notification data on the number of new cases, as currently reported, are a most unsatisfactory index. They are inaccurate and incomplete and so may underestimate or overestimate the actual rates. They may reflect the intensity of case-finding efforts being made from time to time rather than actual epidemiological trends. They are particularly deficient in bacteriological information, as they do not report whether patients are smear positive and/or culture positive, or even whether such an examination has been performed. It would greatly improve comparisons within a country, from one period to another, as well as comparisons between countries, if an internationally agreed form of notification, including the results of standardized bacteriological examinations, could be widely adopted. (Nonpulmonary tuberculosis is even more likely to remain unnotified than pulmonary disease.)

Currently the two epidemiological indices most relevant to measurement of the tuberculosis problem in the community and to programme strategy are:

(*a*) the prevalence of tuberculous patients excreting bacilli demonstrable by direct smear examination—such patients are mainly responsible for transmission of infection and the disease in the community;

(*b*) the age-specific prevalence of tuberculous infection as demonstrated by tuberculin testing.

A comprehensive prevalence survey gives reliable information on the magnitude of the pool of infectious sources in the community. However, such surveys require considerable resources and technical skill. In contrast, the age-specific prevalence of tuberculous infection based on a well calibrated, low-dose tuberculin test can be undertaken in much smaller study populations than those needed for surveys of infectious sources. Tuberculin surveys of a representative sample of unvaccinated children at a specified age (for example, at school entrance age) are therefore the method of choice. Such surveys can be carried out without difficulty in most countries. Their design and statistical interpretation become more complicated in countries where a substantial part of the age group under investigation has been previously vaccinated with BCG, in countries with a high coverage of BCG vaccination at birth, and also in areas with a high prevalence of nonspecific cross-reactions. In the latter situation, double skin-testing with human tuberculin and a tuberculin prepared from a mycobacterium other than *Mycobacterium tuberculosis* has been tried, but the value of such double testing is still under investigation.

Data on the age-specific prevalence of infection (obtained in a single tuberculin survey conducted in a range of age groups) merely reflect the accumulated epidemiological history of the group, but do not give independent information about the variation of infection risk either with calendar time or with age. To calculate these trends separately at least two tuberculin surveys are required, at different times, in the same age groups in the same community.

The Committee noted with approval the comparable quantitative information on the trend of the annual risk of infection that has been collected from a number of high-prevalence and low-prevalence countries, many of which have been surveyed by a single, highly specialized, and skilled international surveillance team. This work has established that in some low-prevalence countries the risk of infection is decreasing by approximately 10% per annum, while in some of the higher-prevalence countries, there has been no evidence of any appreciable change in the annual risk over a number of years.

However, it is often not appreciated that a substantial case load and annual incidence of new infectious cases may occur in the older age groups, even though there is very little transmission of infection in children and young adults.

There is abundant evidence that radiography cannot reveal with any certainty whether shadows are of tuberculous origin ; bacteriological confirmation is necessary for such a determination. Therefore, no definite epidemiological significance can be attached to the so-called " radiological prevalence and incidence rates ".

2.2 Special-risk groups

The epidemiology of groups at special risk is of particular interest to the public health planner because it is neither economical nor operationally feasible to attempt equal case-finding coverage for all segments of the population. To establish that a group is, in fact, a high-risk group, the group must be clearly defined and it is necessary to know its size and the relative risk of contracting the disease for subjects in the group compared with the general population.

The Committee stressed that older adolescents and adults with respiratory symptoms that prompt them to seek medical advice are the highest priority group in which to seek cases—the yield of smear-positive cases is greatest if the symptoms persist for more than 4 weeks.

Other groups known to carry a high risk include the following : persons who have been in close contact with a smear-positive index case, health staff exposed to infection in wards and laboratories, particularly if they have not been protected by BCG vaccination, patients who have had tuberculosis but have had either no chemotherapy previously or inadequate chemotherapy, and persons known to have radiographic abnormalities in the lung of the type termed " fibrotic lesions ", especially if these are large and recently detected. Some migrant groups, elderly subjects living alone and other special social groups, patients with certain concomitant diseases, for example, diabetes, pulmonary dust diseases, and gastrointestinal malabsorption syndromes, alcoholics, and patients on steroids are also subjects at special risk.

2.3 Primary drug resistance

Owing to the wide extension of chemotherapy often with the production of substantial numbers of chronic excretors of drug-resistant organisms, it was at one time feared that primary drug-resistant disease, that is disease produced by resistant organisms, might become a problem that would assume epidemiological importance. The Committee noted that several well conducted surveys, repeated after an interval, have shown that although the level of primary drug resistance is usually higher in developing countries than in technically advanced countries, there has been no general evidence of an appreciable or systematic increase in the levels during the past decade. Indeed, there is evidence that, as the standards of chemotherapy improve, the level of primary drug resistance becomes stabilized. Furthermore, the majority of primary resistance is to a single drug and the response of the patients to standard triple-drug chemotherapy is usually good.

2.4 Atypical mycobacteria

A considerable amount of research has been undertaken for many years into the classification of species of mycobacteria other than *M. tuberculosis* or *M. bovis*, their geographical distribution, and their significance in epidemiology and as a cause of disease. Present knowledge indicates that although skin sensitization to these mycobacteria is often prevalent, especially in tropical countries, disease due to these organisms is rare. However, skin sensitivity to human tuberculin caused by these mycobacteria is a complicating factor in the conduct and interpretation of tuberculin surveys (the relevance to BCG vaccination is referred to later).

2.5 Predictive epidemiology and surveillance

Mathematical models describing the epidemiological course can provide important information on the dynamics of tuberculosis, in terms of infection and disease, and can make it possible to predict the effects of different types of activity, such as BCG vaccination and case-finding plus treatment. They have also paved the way for cost–effectiveness analysis and, with the help of resource-allocation models, for cost–health benefit calculations. Epidemiological models are of particular interest to the epidemiologist, and resource-allocation models to the public health administrator and planner.

Whereas evaluation is concerned with the current events of the programme, surveillance of tuberculosis is concerned with measurement of the long-term trends of the problem. Surveillance can guide the epidemiologist and the public health administrator by indicating whether the problem is increasing, static, or declining. An example of surveillance is the measurement of the trends of annual infection rates. Another example is the incidence of tuberculous meningitis in children, a factor that may be important in deciding the age at which BCG should be given.

Surveillance can either be a continual process or it can be repeated periodically. It requires a system that provides for the collection of pertinent epidemiological data, their orderly consolidation and analysis, and the dissemination of the results to all who need them, particularly those in a position to take action.

Efforts should be made to improve and extend the application of surveillance in tuberculosis control programmes.

3. BCG VACCINATION

The Committee noted with satisfaction that during the last decade the scale of BCG vaccination had increased for several reasons. There had been an increase in the use of direct vaccination (without a prior tuberculin test), and the simultaneous administration of BCG and smallpox vaccination. Furthermore, better vaccines had become more generally available.

The Committee strongly emphasized that due attention should be paid to the quality of the vaccine and to the vaccination technique. It has been clearly demonstrated that BCG vaccines may vary widely, both in terms of their immunogenic properties in animals, and in terms of the proportion of live organisms in the product. The Committee considered that the contradictory results of controlled clinical trials in the past can be reconciled only by accepting that in some trials the protection afforded by the vaccine was low or nonexistent, because of the poor immunogenic capacity of the strain, low viability of the vaccine, or deficiencies in the technique of administration.

The Committee noted that WHO had established formal " Requirements for dried BCG vaccine ",[1] specifying the use of the seed-lot system, and quality control of every batch of vaccine. These requirements provide a framework within which national control authorities and international organizations can formulate more specific requirements.

3.1 The vaccine

A BCG strain used in the production of vaccine should, in animal experiments, resemble vaccines proved effective in controlled trials: it should give a high protection in different animal models and display residual virulence in susceptible animal species. It is now known that both delayed hypersensitivity and acquired resistance to tuberculosis are cell-mediated immune responses that, in animal experiments, occur together and are perhaps expressions of the same process. It is therefore advisable to avoid strains of low allergenicity. Some strains are easier to handle in production than others. However, present day technology makes it possible to prepare viable and reasonably stable vaccines even from strains that are more difficult to handle in production. Thus, immunological criteria can now be given priority when selecting a strain.

The changes known to have occurred in many BCG strains—in morphology, in their protective effect in animals, and in their allergenic effect in man—have arisen through mutation and selection during the maintenance

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[1] *Wld Hlth Org. techn., Rep. Ser.*, 1966, No. 329.

of the strain by serial subculturing. Such changes can be prevented by using the seed-lot system, in which dried BCG is kept for use as seed for the preparation of the cultures from which the vaccine is harvested.

A BCG vaccine should contain as high a proportion of live bacilli as possible, because the dead organisms in partly killed BCG contribute relatively less to the degree of tuberculin sensitivity induced by the vaccine than to the size of the lesion at the site of inoculation. Moreover, killed BCG (without adjuvant) is known to protect very poorly in animal tests. In the past, gross differences have been observed between the viability of vaccines prepared in different laboratories and even between batches of vaccine prepared in a single laboratory. Currently, however, several laboratories have achieved a high and uniform viability in their liquid vaccine, and some also in their freeze-dried vaccine.

Freeze-dried vaccines, when reconstituted, have a lower viability than the liquid vaccines from which they were prepared. Nevertheless, the Committee felt that they are to be preferred under almost all circumstances, because of their vastly superior keeping qualities (including, for some products, substantial heat stability), which simplify shipment and considerably reduce waste. Moreover, quality control can be completed before a batch is released for use.

The Committee emphasized that extensive quality control is crucial in order to obtain an acceptable product and to validate it. Tests are needed (1) at various stages in the production process itself, (2) at the national level as an independent routine check, and (3) at the international level as a baseline for the national control and also as a guarantee of the quality of supplies available internationally.

The Committee noted with satisfaction that WHO has set up an international control system. At present this service is used primarily for vaccines supplied by or through UNICEF, random samples of the vaccine being checked from time to time to ensure the maintenance of uniform quality. This system is also available to producers and national control authorities, as well as to governments importing vaccine. The Committee expressed the hope that this control system will be used increasingly by all who produce or import vaccine.

It takes great technical skill and considerable investment in equipment to produce a good quality freeze-dried BCG vaccine and to perform locally the required quality control tests. The manufacture in a small laboratory of dried BCG for which there is a limited demand usually results in a poor and expensive product. The Committee therefore favours the closure of such laboratories. It considers that it is desirable to concentrate technical support at the international level on the limited number of carefully chosen laboratories that have the prospects of covering the needs of large popula-

tions. A reduction in the number of laboratories would also facilitate both national and international control.

3.2 The response in man

It has long been known that the degree of tuberculin sensitivity induced in man by BCG varies with the dose of vaccine. The limited evidence that can be extracted from controlled trials in man suggests that the degree of protection is also a function of the dose of BCG. The aim is, therefore, to administer the highest dose that is tolerated, in the sense that it produces an acceptably low rate of local and regional adverse reactions. Newborn and young infants are especially prone to develop suppurative lymphadenitis, the frequency of which is known to increase sharply with dose. The Committee recommends, therefore, that the dose for young infants should be lower than for older children and adults.

Sensitization by atypical mycobacteria may be very common in tropical and subtropical populations. Epidemiological observations in man indicate that this sensitization is associated with a certain degree of protection against tuberculosis. Laboratory experiments have confirmed that atypical mycobacteria may induce some protection against tubercle bacilli, but that such protection is weaker than that induced by a potent BCG vaccine, and that BCG vaccination is capable of increasing the level of protection thus acquired up to that induced by BCG alone, though not higher. In persons with low-grade tuberculin sensitivity (induced by atypical mycobacteria) it is possible, by administering a potent BCG vaccine, to raise the level of tuberculin sensitivity. The Committee decided that it is reasonable to conclude that potent BCG vaccination increases the level of protection in persons sensitized by atypical mycobacteria. Conversely, a vaccine would be useless if it were so weak that it did not increase the level of protection beyond that already acquired from sensitization by atypical mycobacteria.

The Committee emphasized that intradermal vaccination by syringe and needle remains the most precise way of administering the desired dose. Intradermal injection by jet injector is inaccurate and expensive. Percutaneous vaccination is even less accurate and, moreover, with this method it is not possible to introduce the desired high dose of vaccine into the skin. The available evidence on percutaneous vaccination under field conditions indicates major variations between vaccinators, so that training and supervision are likely to be as necessary for percutaneous as for intradermal techniques.

An instrument known as the bifurcated needle has greatly facilitated percutaneous vaccination in the smallpox eradication programme. Its use

for BCG vaccination also appears attractive because of its simplicity, and operational and logistic advantages, at least for simultaneous BCG and smallpox vaccination. Unfortunately, even when using the strongest percutaneous vaccines the maximum amount of BCG that can be inoculated is only about one-third of that usually recommended for intradermal injection. The Committee noted that there is a need to test the performance of the method under conditions of mass field use and also to develop a sufficiently strong vaccine at an acceptable cost.

The Committee concluded that prolonged experience with direct vaccination of whole age groups without prior tuberculin testing has fully confirmed the results of the numerous pilot studies that found this method to be safe and acceptable.

A number of studies indicate that the immune responses are not reduced and that the rate of complications is not increased if several immunization procedures are applied simultaneously at separate sites. Thus BCG has been given together with immunization against smallpox, measles, yellow fever, diphtheria, pertussis, and tetanus. The Committee noted that the simultaneous administration of BCG and smallpox vaccines at separate sites is now a well established practice, usually undertaken by smallpox vaccinators. This has increased the coverage achieved, and reduced the cost per vaccination.

4. CASE-FINDING AND TREATMENT

The object of tuberculosis control is to break the chain of transmission of infection. This can be achieved by detecting the sources of infection as early as possible and rendering them noninfectious by chemotherapy. Transmission is maintained in the community particularly by subjects whose sputum is so heavily positive that tubercle bacilli can be detected by smear microscopy.

4.1 Case-finding methods

Case-finding methods should not be judged solely on their technical merits but also on their public health implications. This is because case-finding is not an end in itself. It is a preliminary to treatment and cure. The expansion of a case-finding programme should be based on the criterion of the cost per case found, but expansion should not proceed ahead of the ability of the service to deliver effective chemotherapy to the patients and cure them.

4.1.1 *Practical methods*

The Committee considered that the following practical methods of case-finding offer the best prospects of producing significant yields :

(1) the examination of patients who present themselves with relevant symptoms to any health facility,

(2) increasing the awareness of the community, the medical profession, and all cadres of staff involved in the programme concerning the importance of symptoms referable to the respiratory system, notably persistent and productive cough, bloodstained sputum, and chest pain, especially if they have been present for more than 4 weeks,

(3) the examination of contacts, especially if they have symptoms,

(4) the bacteriological examination of patients who have had a radiographic examination of the chest for whatever reason, if it shows a lesion with a possible tuberculous etiology,

(5) the examination of immigrants and foreign workers coming from high prevalence areas—the Committee strongly recommends that their treatment should be the responsibility of the host country.

The Committee was of the opinion that well organized outpatient chemotherapy, especially if provided free of charge, would attract symptomatic cases from far and wide, for the reputation of a good service spreads rapidly.

4.1.2 *Mass radiography*

The Committee noted that mass miniature radiography is a very expensive screening procedure for tuberculosis, even when the prevalence is high. Other disadvantages of mass radiography are as follows : (1) it contributes only a small proportion of the total number of cases found ; (2) it has no significant effect on the occurrence of subsequent smear-positive cases, as they usually develop so rapidly that they arise between the rounds of mass radiography examinations (thus it follows that case-finding and treatment facilities should be constantly available for an indefinite period to come) ; (3) it requires the services of highly qualified technicians and medical staff who could be better used in other health service activities ; and (4) the apparatus or the vehicles used to transport it, are often out of service because of mechanical breakdown for months on end, especially where spare parts are in short supply. The Committee concluded that the policy

of indiscriminate tuberculosis case-finding by mobile mass radiography should now be abandoned.

4.1.3 *Tuberculin testing*

The Committee considered that large-scale tuberculin testing for the identification of the sources of infection of recent converters has little merit in a tuberculosis control programme.

4.1.4 *Diagnosis*

Bacteriological investigation of sputum is a direct way of diagnosing tuberculosis, since the demonstration of tubercle bacilli is conclusive. Such investigation is necessary to establish the tuberculous etiology of abnormalities found on chest radiographs. The wide observer variation and differences in interpretation of radiographic appearance have been repeatedly demonstrated. Furthermore, the Committee pointed out that when treatment for tuberculosis is initiated on the basis of radiographic findings alone, a substantial proportion of patients are treated unnecessarily. This wastes the resources that should be concentrated primarily on the treatment of infectious cases. It throws needless strain on understaffed and underfinanced treatment services and unnecessarily exposes many patients to loss of their job, loss of their home, and to serious social stigma. Hence, the importance of making a bacteriological diagnosis.

4.1.5 *Bacteriological procedures*

The role of the bacteriological examination of sputum in the diagnosis of tuberculosis and the control of chemotherapy has been growing in the past decade.

From the point of view of their value in a tuberculosis control programme, bacteriological techniques may be ranked in the following order : examination of direct smears, culture and, lastly, sensitivity testing.

The first aim of a bacteriological service in a developing country should be to perform sputum examinations by microscopy on a large enough scale to permit the accurate bacteriological diagnosis of every smear-positive case and next to follow the progress of chemotherapy. Particular attention must be paid to careful instruction of the patient to ensure the collection of good specimens of sputum. Specimens should be transported in a suitable container as rapidly as possible for examination. Bright-field microscopy (for instance, using Ziehl-Neelsen staining) is most suitable for peripheral laboratories. Fluorescence microscopy would be preferable

in larger laboratories because it allows more specimens to be examined in the same time and is economical. The number of cases detected by sputum smear examination depends on the number of specimens examined per patient. If the prevalence of smear-positive patients is high in the patient population, the examination of smears from several specimens, especially an early morning one or an overnight collection, will detect a large proportion of the infectious cases in the community.

The examination of cultures in addition to smear examination will add to the number of patients with a confirmed diagnosis of tuberculosis, especially in those who are not excreting large numbers of bacilli. However, culture services should be provided only when a reasonably high proportion of the smear-positive cases in the country are being discovered and treated by chemotherapy and then they should be provided only in large laboratories. Egg media (e.g., Lowenstein-Jensen and Ogawa) are most widely used. Concentration before culture improves the sensitivity of the method. Simple methods of identifying cultures as *M. tuberculosis* are desirable, particularly in laboratories in the tropics where contaminatory mycobacteria are common.

The Committee considered that sensitivity tests are mainly of value for epidemiological purposes and for selecting standard regimens for large-scale chemotherapy programmes in individual countries. In the individual patient they are of most use when the smear and culture examinations suggest that chemotherapy has failed. However, no laboratory should embark on sensitivity testing until adequate skilled staff, equipment, and interest exist to sustain a high standard of work.

Steps should be taken to prevent infection of the staff working in laboratories. The risk of infection is higher in laboratories undertaking culture and sensitivity tests than in those doing smear examinations only. The provision of ventilated inoculation cabinets is the most effective single safety precation.

4.2 Chemotherapy

The Committee emphasized the importance of giving adequate chemotherapy to every patient with infectious pulmonary tuberculosis. Such treatment meets the expressed needs of patients who present with symptoms and saves many lives. Furthermore, it reduces transmission of infection in the community. Chemotherapy should be available, free of cost, for every patient detected. In the developing countries, widespread treatment services may be feasible only if careful attention is paid to the rational utilization of the available funds and health personnel.

4.2.1 *Ambulatory treatment*

The WHO Expert Committee on Tuberculosis in its last report considered that it was incumbent on those advocating the superiority of institutional treatment to conduct studies to determine whether their contention was substantiated by objective evidence. This conclusion was reached after reviewing the world literature on controlled comparisons of domiciliary and institutional treatment of pulmonary tuberculosis, considering the immediate response to treatment, the risk of subsequent relapse, and also the risk to contacts. Since then several further studies have been reported. All have confirmed the lack of necessity for institutional treatment. The Committee therefore reiterates the previous recommendation that the financial resources and manpower available for tuberculosis control be used to organize efficient and widespread ambulatory programmes rather than to support hospital treatment.

4.2.2 *National review of sanatorium services*

The Committee noted with concern the adherence to outmoded long-term sanatorium treatment in some technically advanced countries and recommended that the national authorities should review the reasons for the retention of traditional sanatorium services despite the dramatic progress of chemotherapy in the last 20 years. In this connexion the Committee emphasized that it is the responsibility of the national authorities to make alternative careers available to sanatorium physicians.

4.2.3 *Effective regimens*

In selecting the regimens to be used in national programmes due weight must be given to the efficacy, toxicity, acceptability, bulk, and cost of the available drug combinations. The Committee emphasized that the combinations and dosages used should be those established in well conducted controlled clinical trials. The main drugs to be considered in national tuberculosis programmes are isoniazid, streptomycin, *p*-aminosalicylic acid (PAS), and thioacetazone, with which highly effective and relatively inexpensive regimens can be formed. More recently rifampicin and ethambutol (the former being particularly expensive) have been introduced in affluent countries, but cost is often decisive in choosing standard regimens for widespread use, even in them.

4.2.4 *Regularity of chemotherapy*

The Committee stressed that modern chemotherapy should cure almost all newly diagnosed patients if an effective regimen is provided for an

adequate period of time and if regular ingestion of the drugs by the patient is secured. Careful supervision is required to ensure that a patient actually receives the full course of a standard self-administered regimen, including surprise checks of the patient's stock of medicaments and the examination of urine specimens for the antituberculosis drugs. Such supervision is, however, often not possible. An effective alternative approach is to give intermittent regimens under full supervision as described in section 4.2.7.

4.2.5 *The importance of intensive chemotherapy at the beginning of treatment*

The early stages of chemotherapy are crucial for the final outcome of treatment, especially for infectious patients. The aim should be, if supplies of the standard drugs are plentiful, to start with an initial course of triple-drug chemotherapy (including isoniazid) for periods of from 1 to 3 months, followed by a two-drug regimen (including isoniazid). Intensive chemotherapy has the advantage of being more effective in eliminating drug-sensitive bacilli, and in minimizing the influence of initial drug resistance of the strains. Hence, the intensive phase is particularly important where initial drug resistance is prevalent. Even after an initial intensive phase regularity of administration is important in the continuation phase.

4.2.6 *Thioacetazone as an inexpensive oral companion drug to isoniazid*

Doses of 300 mg of isoniazid and 150 mg of thioacetazone in patients weighing 35 kg or more (these dosages are important because they usually combine effectiveness and low toxicity), in one daily dose combined in a single tablet are effective and are widely used. In many communities this combination has an acceptable level of toxicity. This combination is inexpensive, has good keeping properties even in tropical conditions, and, being small in bulk, is convenient both to dispense and for the patient to take. The Committee noted that a vitamin and antihistamine additive, which was claimed to reduce the frequency and severity of adverse reactions, was ineffective, substantially increased cost, and impaired the keeping properties of the preparation.

4.2.7 *Directly supervised intermittent chemotherapy*

Fully supervised intermittent chemotherapy with appropriate drugs is not only therapeutically highly effective but carries benefits in terms of lower toxicity and cost. Full supervision overcomes undetected irregularity inherent in long-term self-administration of drugs. Failure of a patient

to attend for a supervised dose is immediately apparent and appropriate action can be taken forthwith. The standard intermittent regimen is 1 g or 0.75 g of streptomycin plus isoniazid in a single dose of approximately 15 mg per kg bodyweight, given together on 2 days each week, preferably with 5–10 mg of pyridoxine to prevent peripheral neuritis.

The Committee discussed the need for fully oral, standard, intermittent regimens and noted the promising results with twice-weekly PAS plus high-dosage isoniazid.

As with daily regimens, intermittent regimens should, whenever possible, be preceded by a daily intensive phase of chemotherapy for 1–3 months.

Once-weekly continuation regimens cannot yet be recommended for general use but the Committee noted that promising research in this field was continuing.

4.2.8 *The duration of chemotherapy*

It is still the practice in many countries to prescribe chemotherapy for a minimum of 18 months to 2 years for bacteriologically confirmed cases. There is increasing evidence that such a duration of treatment is unnecessarily long. The Committee emphasized that the benefits of prolonging chemotherapy beyond a year are small. It is much more rewarding to concentrate efforts on ensuring that every patient continues on the regimen for 1 year without interruption.

The use of short-course regimens of chemotherapy, some lasting only 6 months, is still at an experimental stage.

4.2.9 *Retreatment regimens*

The need for retreatment should be avoided as far as possible by making every effort to ensure the highest standards in the original treatment. However, if the original treatment fails, several choices of retreatment regimen are now available. When isoniazid and thioacetazone strengthened by streptomycin in the initial intensive phase is the usual regimen, a combination of streptomycin, PAS, and pyrazinamide is still effective in retreatment and has a relatively low toxicity. Traditional regimens containing ethionamide, pyrazinamide, and cycloserine, are expensive, toxic, and usually require hospitalization. Where resources permit, they are being replaced by regimens of rifampicin and ethambutol.

4.2.10 *Initial drug resistance*

The Committee emphasized that the importance of initial drug resistance as a cause of treatment failure has been much overrated. Failure to respond

to the standard regimens of chemotherapy because of initial drug resistance is more likely to occur in patients with strains resistant to two or all three of the drugs in the regimen than in those with resistance to one drug only. Patients with multiple-drug-resistant strains, however, represent only a very small proportion of the total even in communities in which drug resistance is known to be common. There are a few areas in Africa where thioacetazone-resistant strains (of a type termed *M. africanum*) are reported to be so common as to make regimens containing thioacetazone unsuitable.

4.2.11 *Observations during chemotherapy*

Bacteriological investigations are much more informative than radiography in following the progress of chemotherapy. If bacteriological facilities are limited, examination of sputum smears from 6 months onwards will detect the majority of failures whether they are due to persisting bacteriological positivity or to relapse. However, culture examination, in addition, may provide earlier evidence of failure and enable sensitivity tests to be carried out.

The main reason for carrying out sensitivity tests on cultures from the individual patient during primary chemotherapy is to distinguish between failure of a regimen because of the emergence of drug resistance and failure due to inadequate drug ingestion. In the latter case, the organisms often remain drug-sensitive and will still respond to the original regimen, if this is well supervised. Thus the planning of further chemotherapy can be assisted by simple tests of sensitivity, particularly sensitivity to isoniazid. Sensitivity tests to the drugs used in retreatment regimens can also be of assistance in individual patients who do not respond to them, but there are relatively few laboratories in the world capable of performing tests of sensitivity to some of these drugs in a reliable manner.

4.2.12 *Follow-up*

Increasingly potent regimens are now available, and, in the light of modern knowledge, they can be administered in a better organizational framework than in the past. In consequence, when patients complete the prescribed course of chemotherapy subsequent relapse should be very rare. The Committee therefore considers that much less emphasis is necessary than in the past on the follow-up of patients after their treatment has been completed. Patients can be advised to return if the symptoms recur. This is now being appreciated even in the technically advanced countries. With few exceptions, it is more rewarding to concentrate on organizing case-finding programmes and improving the supervision of original chemotherapy.

4.2.13 *Preventive treatment*

The Committee emphasized that a policy of preventive treatment (often termed chemoprophylaxis) is irrational, even for special risk groups, unless the treatment programme for patients suffering from infectious tuberculosis is widespread and well organized, and achieves a high rate of cure.

Although isoniazid can be considered a safe drug in the treatment of frank tuberculosis, its side effects must be viewed in a completely different light when it is administered to persons who have only a small chance of deriving benefit. In chemoprophylaxis programmes, cases of isoniazid-associated hepatitis are reported in increasing numbers, and some have proved fatal.

The benefits must be weighed against not only the side effects but also the inconvenience to the individual, including the social and economic penalties of being labelled " high risk " or " tuberculous ". Furthermore, the difficulty of persuading apparently healthy individuals to accept long-term medication, and the substantial cost (manpower and other resources) must also be taken into consideration.

For these reasons, the Committee considered that preventive treatment was not suitable for mass application in a community health programme.

5. THE NATIONAL TUBERCULOSIS PROGRAMME

The national tuberculosis programme is a methodical approach within the country health programme designed to reduce progressively the tuberculosis problem in the community.

Since reliable diagnostic tools and efficacious preventive (BCG) and curative (chemotherapy) methods are available and because they can be both simple and inexpensive, the control of tuberculosis deserves a high priority on the list of rewarding health programmes. An effective national tuberculosis programme can be delivered under any situation, provided planning and application are guided by a clear understanding of the epidemiological, technical, operational, economic, and social aspects.

The Committee discussed the organization of national tuberculosis programmes and the following observations were made.

The programme must be country-wide. Numerous studies have shown that tuberculosis is usually fairly evenly distributed between villages and towns. In countries where the population is largely rural, as in most developing countries, the bulk of the tuberculosis problem is found in the rural areas. However, the tuberculosis services in these countries are almost

always centred in the cities and are thus out of contact with the bulk of the problem.

The programme must be permanent. The majority of the world's adult population has been infected by tubercle bacilli. From this pool, new cases of tuberculosis will therefore continue to develop for several decades to come. Hence, no crash programme or one time endeavour can substitute for the delivery of a permanent programme.

The programme must be adapted to the expressed demands of the population. The expressed demand for tuberculosis services reflects the amount of human suffering and economic deprivation in the community. To be successful, a programme should be in consonance with the current attitudes and behaviour of the community, meet the public demand, and, in particular, be convenient for the consumer rather than merely for those providing the services. Accessibility and acceptability of the programme are important aims. The public will have confidence in the services only if they are effective.

The programme must be integrated in the community health structure in order to meet the above-mentioned requirements. The programme must be developed as a well balanced component of the country health programme and within the available resources. Attempts to establish an independent specialized service for tuberculosis are irrational in developing countries. Such a service would absorb a disproportionate share of the limited trained manpower and financial resources available, at the expense of other essential health services. It is equally irrational to maintain specialized tuberculosis services in countries where the problem has been greatly reduced. A network of permanent health services is required to which people can go if they feel ill. The network should include the private practitioners as well as the outpatient departments of hospitals, the health centres, dispensaries, and health posts. With the simplified and standardized technology available today, tuberculosis prevention measures and diagnosis and treatment can be carried out at any health institution, and the control measures can be carried out by health auxiliaries, if they are properly trained and supervised. Simplification and standardization of techniques and procedures have made it possible to transfer the expert skill of a few specialists to the large numbers of health personnel, including auxiliaries, who have to deliver the programme.

The establishment of the national programme in the field, demands a continuous and long-term effort. At the central level there must be a single directing authority with responsibility. In most programmes there are three levels with different, clearly defined responsibilities as follows : at the central level—policy making, planning, programming, coordination,

programme training, direction, and evaluation ; at the intermediate level—supervision and evaluation of the peripheral and referral services, and in-service training ; and at the peripheral level—the actual delivery of the services.

5.1 Planning and programming

Tuberculosis programmes have in the past evolved simply by merging certain services and control activities. In such programmes, planning was essentially pragmatic, and often guided by personal bias. This resulted in unrealistic targets, imbalance, and lack of coordination between the various programme elements—the opposite of an integrated service. The Committee therefore considered that systematic planning is essential if meaningful operational objectives and rational policies are to be established. This would imply the programming of the operational steps for implementation, monitoring, and evaluation.

The planning of a national tuberculosis programme should be based on data derived from a thorough situational analysis. This should provide information on demography (including ethnic and other important groups and their particular patterns of behaviour towards health and illness), on communications and administration, school attendance, community and health development programmes, the structure of the health services and their coverage of the population, the availability of professional, auxiliary, and voluntary manpower, and on other resources available at the central, intermediate, and local levels.

A limited baseline sample survey may be needed to provide the necessary epidemiological and operational data. Planning then consists of organizing this information into a schedule for the development of anti-tuberculosis activities, both preventive and curative, within the basic health services to cover the population within a reasonable period of time. Based on this schedule, a programme should be formulated that specifies the approach to be followed, the allocation of resources, the personnel to be trained, and for each health agency in the community the area it should cover. The operational objectives of the programme should be clearly stated.

In order to prepare the plan of action, the main events as well as the activities required to achieve them, must be enumerated precisely in their logical sequence.

5.2 Selection of technical policies

The selection of technical policies should be made on the basis of priorities, which, of course, may change with time and from place to place.

The components to be considered are case-finding and treatment, and BCG vaccination. The emphasis to be given to either component depends largely on the epidemiological situation and the resources available, but the Committee felt that both components should be initiated in almost all situations.

5.2.1 *Case-finding and treatment*

The case-finding and treatment programme should be developed as an entity. Treatment should be free of charge and should be primarily ambulatory. The abandonment of the dependence on sanatorium treatment and hospitalization means that treatment is automatically decentralized and will be undertaken in the numerous health facilities where the patient presents with symptoms. Thus the very existence of an ambulatory programme implies the development of a decentralized curative service.

In a logical and efficient sequence of priorities, the first priority would be to provide facilities for direct smear examination of sputum from persons who, of their own volition, present with symptoms and to provide adequate treatment for those who are found to excrete tubercle bacilli. In such a programme, patients with persistent symptoms but whose sputum does not contain bacilli should be followed up ; treatment with antituberculous drugs would be given only if the diagnosis can be confirmed bacteriologically.

Effective standard regimens should be made available, for daily and for supervised intermittent chemotherapy, and if possible, drugs should be provided for an initial intensive phase.

The first phase of the programme should aim at covering the entire country with conveniently situated facilities where patients can go to have their sputum examined and obtain treatment. However, the programme should not be expanded to the detriment of the quality of therapy.

When the entire country is adequately covered with an effective curative service that satisfies the demands and needs of the population, an active expansion of case-finding should be initiated. A health education programme should then be instituted to increase awareness of symptoms among the public.

Subsequently culture facilities for the bacteriological examination of sputum should be introduced. To a certain extent these facilities will also help to meet the needs of the population, although it should be borne in mind that the patients detected in this way are less infectious than smear-positive cases.

Smear examination and, at a later stage of development, culture can be used to assess the results of treatment. Patients who remain consistently positive require retreatment. Such patients who have been irregular in

their treatment may well respond again to the original regimen if it is well supervised, otherwise a change of chemotherapy will be required. Sensitivity testing, especially to isoniazid, may provide guidance in the choice of an appropriate retreatment regimen. The Committee reiterated that retreatment should not be allowed to be a drain on the available resources for tuberculosis control and should not be instituted until a high level of success has been achieved in the original treatment of newly diagnosed patients.

The examination of high-risk groups should not be carried out at the expense of the development of adequate diagnostic and treatment services for the whole country.

5.2.2 *BCG vaccination*

When BCG vaccination is initiated in a country, or if the coverage obtained in an existing programme is inadequate, an intensive mass campaign is indicated, with the object of covering the eligible population (usually all persons up to 15 or 20 years of age) in a short time. Experience indicates that a coverage of 70–90% is a feasible target. Thereafter, a programme integrated with the general health services is more likely to achieve and maintain a high coverage. The Committee felt that the same staff should undertake preventive measures against several diseases, practising simultaneous immunization whenever justified and expedient.

The Committee emphasized that where infant tuberculosis is a problem, the widest possible coverage with BCG vaccination should be ensured as early in life as feasible.

Young adults are often particularly exposed to primary infection with tuberculosis. Even more important, young adults are more likely to develop the disease soon after infection than are children of school age. In contrast to infants and young children, they develop the infectious type of tuberculosis. Hence, the maintenance of immunity, by vaccination at the school-leaving age, can be expected to yield benefits not only in terms of disease prevention but also in breaking the chain of transmission.

Where the risk of infection is very high, vaccination at the usual school-entrance age may be justified as under these circumstances most infection will take place during the first few years in school. At the other extreme, if the risk of infection in a country is known to be declining rapidly, vaccination at the school-entrance age may also be the best policy, as a large proportion of the total infection during the lifetime of each cohort will take place before the school-leaving age is reached.

Vaccination at school age (as referred to above) should be undertaken irrespective of vaccination at birth, since the immunological response of infants is poor and it has never been demonstrated that the reduced dose of BCG usually given to the newborn will induce a lasting significant level

of protection. Apart from the revaccination of schoolchildren who were vaccinated at birth, revaccination is indicated in groups of persons known to have been vaccinated inadequately, e.g., with a product that was later demonstrated to have been of a low potency.

Tuberculin testing before vaccination always reduces coverage and more than doubles the cost. In situations where cost is of little importance, the prevalence of infection is generally low. The Committee therefore favoured direct BCG vaccination under almost all circumstances, especially at revaccination. In deciding on the age-limit for direct vaccination, the age-specific prevalence of infection, as determined by surveillance, should be taken into account.

5.3 Implementation

A sound starting point of a national tuberculosis programme is a strong directing unit with central authority under the ministry of health. The necessary epidemiological data on the magnitude and distribution of the tuberculosis problem must be made available so that the unit can carry out its functions of programme implementation and direction. It is valuable to employ modern management techniques in scheduling and monitoring the implementation of the plan of action.

Development of the programme usually proceeds by areas. It should be started in a single area (e.g. a district) that provides opportunities for practical field experience and training. The practicability and the actual flow of the programme under field conditions should be evaluated from the outset because this provides important operational information needed to readjust the programme and to extend it to other areas.

Programme implementation is the main responsibility of the managerial teams, specially trained in all technical and operational aspects of the programme. They will spend most of the time in the field and at the peripheral level. Their activities will include in-service training of staff, distribution of equipment and supplies, and the technical evaluation of the programme components. Successful programme implementation will only be possible if the necessary equipment and supplies (which should be commensurate with the programme adopted) become available in good time and a reliable and continuous supply line is ensured.

It is essential to establish simple but effective and meaningful recording and reporting systems for the purpose of programme monitoring and evaluation and for further planning.

The difficulties encountered during the implementation of the programme, and the achievements of the programme, should form the basis for discussion at " workshops ". In addition, prior to implementation, or at an early stage, a national seminar should be held for all cadres of per-

sonnel involved in the national tuberculosis programme, directly or indirectly. It is essential that representatives of other health sectors should participate in such a seminar (e.g., those concerned with maternal and child health, other communicable diseases, health laboratory services, manpower development, and health education) as well as teachers of tuberculosis and of preventive and social medicine in medical and nursing schools. Appropriate voluntary associations should also be invited to participate in view of their significant complementary role in community-oriented health programmes.

5.3.1 *Education and training*

The Committee emphasized that adequate training is of crucial importance for all categories of health personnel participating in the national tuberculosis programme. In this training much more emphasis should be put on the community aspects of tuberculosis and not mainly on the clinical aspects, as at present.

The Committee concluded that it is important that some basic information on national tuberculosis programmes should be added to the curricula of medical and nursing schools. Education and training should be programme-oriented and practical and should include field training.

The training of key medical staff should be undertaken at international or national training centres. Since these individuals will be responsible for the planning, implementation, and evaluation of the national tuberculosis programme, training should be multidisciplinary and should include the social sciences and educational and management technology.

Members of the managerial team who are responsible for the implementation of the programme, including instruction and supervision of peripheral field staff, should be trained at a national centre. They should, in principle, be trained as a group, since the aim is to weld them together into a well coordinated team. In addition to tuberculosis control and supervisory and evaluation techniques, the training should include educational and management technology, not necessarily limited to tuberculosis.

In the training of health centre staff, each task should be clearly specified, with details of what should be done, how it should be done, who should do it, and when. The training of peripheral staff will, of necessity, be largely given on an in-service basis. The training of laboratory staff has been referred to by the WHO Expert Committee on Health Laboratory Services.[1]

The Committee emphasized the importance of the periodic visits by the members of the mobile managerial team to the peripheral workers.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1972, No. 491.

These visits constitute a form of supervision combined with on-the-job training and retraining, and also provide an opportunity to check performance and to correct any deficiencies.

Periodic national seminars have proved to be educationally valuable and are helpful in maintaining the active interest of public health administrators, medical teachers, and health workers from other disciplines, as well as the voluntary agencies participating in the national tuberculosis programme.

Refresher and orientation courses should be held, particularly for physicians, with the object of strengthening active professional support for the national tuberculosis programme.

The Committee emphasized the necessity of regular training at all levels.

5.3.2 *Organization of laboratory services*

When organizing bacteriological facilities in relation to tuberculosis, the object is to provide a service over as wide an area of the country as possible, while maintaining efficient and economical technical methods. The first priority in such a service is the examination of direct smears of sputum.

In the fifth report of the WHO Expert Committee on Health Laboratory Services,[1] three types of laboratory were recognized :

(1) Peripheral : employing 2–3 persons capable of using simple diagnostic methods under supervision, especially microscopy, for several diseases.

(2) Intermediate : multidisciplinary, but without sections specializing in specific diseases. These laboratories were considered to be of key importance.

(3) Central laboratories.

Within this framework the majority of smear examinations for tubercle bacilli are usually done at the peripheral and intermediate level. Cultures, simple identification tests for *M. tuberculosis*, and tests for antituberculosis drugs in urine are carried out by the intermediate and central laboratories, while sensitivity testing should be done only at the central laboratory.

The following functions will, in the main, be the concern of the central laboratory, though some may be delegated to the intermediate level :

(*a*) assistance to the programme directorate in the planning of the national programme ;

(*b*) central facilities for surveillance and epidemiological studies, such as surveys of the prevalence of drug resistance and of results obtained in the treatment service ;

(*c*) training of technicians and the maintenance of their skill by regular personal contact : for this purpose the central laboratory should have a service section ;

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1972, No. 491.

(*d*) provision of assistance in the choice and maintenance of laboratory equipment ;

(*e*) quality control for technical procedures in the more peripheral laboratories ; and

(*f*) research, often aimed at the solution of practical problems within the country.

5.3.3 *Organization of ambulatory chemotherapy*

The major problem of chemotherapy is to ensure that patients receive their regimen regularly throughout the period of treatment. The failure rate of standard regimens in developing countries may be high and is by no means negligible in many technically advanced countries. This is often due to patients completely stopping attending for treatment, many of them shortly after the start of chemotherapy. Although others attend regularly, they may not continue to take their medicaments regularly while on a self-administered regimen, and they may even stop taking them completely.

A. *General methods*. Regularity in drug intake may be promoted by explaining adequately at the time of diagnosis and on several occasions subsequently both to the patient and his family the nature of the chemotherapy, the duration of the course, and the need for regularity. The patient's address should be obtained so that if a patient fails to attend, the appropriate action can be taken promptly. Other addresses that are valuable include the patient's alternative addresses, addresses of other family members, his employer, friends who are frequently visited, and his children's schools.

The service must be organized so that patients are seen rapidly and efficiently when they attend, and an appointment system is essential so that efforts can be made to trace patients who fail to attend. This should be done without delay. Each treatment centre should nominate a staff member to be responsible for tracing those who fail to attend : the alternative of using postal reminders is inevitably much slower and lacks any sense of urgency. Finally, it is important that the community should be involved in the programme, including its leaders, such as village elders, tribal chieftains, or other influential persons, and the welfare organizations, including the voluntary agencies and the laity.

B. *Self-administered regimens*. For patients on self-administered regimens, arrangements should be made for a family member to watch the patient take every dose ; failing this it may be possible to involve a responsible neighbour. Further, the patient's regularity can be monitored by surprise visits to his home, by counting his stock of tablets and/or by collecting a urine specimen to test for antituberculosis drugs or their metabolites.

C. *Fully supervised intermittent regimens*. The administration of fully supervised intermittent chemotherapy should not be given solely in main clinics but be decentralized to health centres, rural health units, dispensaries, welfare clinics, hospitals, factory clinics, general practitioners, mobile services, lay supervisors, etc., so that the patients do not have too far to travel. In rural areas the local market day may offer a convenient opportunity for patients to attend a special treatment station. To gain cooperation, the location of the treatment facility must be convenient for the patient, and the hours during which the supervised chemotherapy is available must also be convenient, so that patients can receive their doses on the way to work or on the way home, or in the lunch hour. A patient in employment should not be expected to lose time from work to receive supervised chemotherapy. The responsibility for following the progress of this type of therapy need not necessarily be as decentralized as the drug administration. The patient's progress should be reviewed from time to time by the staff in the area with the best knowledge of tuberculosis treatment.

Retreatment should not be allowed to compete for the resources available for tuberculosis control until a high level of success has been achieved in the original treatment of newly diagnosed patients. Further, a satisfactory organizational framework is essential, not just for original treatment but also for retreatment if a high level of success is to be achieved.

5.3.4 *Organization of BCG vaccine production*

The Committee reiterated the importance of adequate planning in relation to the preventive component of the national tuberculosis programme. The Committee considered that the choice between importing BCG vaccine and producing it locally should be guided by the requirements for such production listed below.

For the production of freeze-dried BCG vaccine, whether on a small or large scale, a certain critical minimum of accommodation, staff, equipment, and quality control is necessary, the following being essential:

The building should include separate sterile premises, with a sterile air supply at greater than atmospheric pressure, and constant temperature. These sterile premises should comprise several laboratories with anterooms for subcultivation, homogenization, dispensing into ampoules, freeze-drying, and ampoule-sealing. In addition, there must be 1 semisterile room for sterility tests and quality control; 2 or 3 rooms for colony counting and microscopy, and for the vacuum-testing, labelling, and packing, of ampoules; 2 rooms for washing glassware, sterilization, and media-production; 1 refrigerated room for storage of vaccine; 1 or 2 offices; and several service rooms such as a staff rest room, wardrobe, showers, lavatory, and store room (for safety reasons, none of these rooms can be shared with other departments). An animal house containing at least 2 rooms is required.

In addition to the basic equipment needed to prepare liquid vaccine, the following specialized and expensive plant is required ; machinery to supply sterile air, a very complicated type of freeze-drying plant, sterile work stations with laminar airflow, and low temperature refrigerators. With a limited production, hand-sealing of ampoules is feasible. If the other machinery and premises are fully utilized, automatic sealing machinery will be necessary.

The full-time staff should comprise at least 2 professional staff (chief and deputy chief), 4 or 5 technicians, 6 or 7 unskilled workers, 1 secretary-typist, 1 clerk for shipping, and 1 caretaker for the animals.

It is usual for a small laboratory to have 1 or 2 freeze-driers with a total space for 2000–3000 ampoules. This number is also within the daily capacity of a single automatic sealing machine. Thus it is reasonable to expect an annual production of 200 000–400 000 ampoules. Taking as an average 10 vaccinations per ampoule, this would suffice for 2–4 million vaccinations or, depending on the organization and coverage of the vaccination programmes and assuming an annual birth rate of 3–4%, the likely needs for a total population of 50–100 million.

5.4 Evaluation

The Committee considered that continual programme evaluation is necessary to provide a feedback of quantified information. Further, evaluation must constitute an integral component of the programme and should be built in right from the beginning.

5.4.1 *Evaluation of national tuberculosis programmes*

The Committee noted that techniques are now available for evaluating the epidemiological, technical, operational, and economic aspects of national tuberculosis programmes. Although the establishment of a comprehensive evaluation system is a lengthy and complicated process, evaluation undertaken at an operational level is in itself valuable and yields results early in the programme. The Committee recognized that evaluation requires skilled personnel specially trained in all the techniques and procedures employed in the national tuberculosis programme, and with considerable managerial experience.

The Committee recommended that the mobile teams responsible for evaluation should also be concerned with the identification of technical and operational deficiencies and components of the programme presenting special problems, the consideration of possible alternative techniques, as well as the provision of on-the-spot training. In this way evaluation assumes functions of supervision and training and much of the reporting of routine statistics is obviated.

In order to determine the success of the control programme in achieving the predetermined objectives, evaluation should provide quantitative information relevant to both the health benefit derived from the different programme components and the resources employed.

The Committee reviewed the indicators that are suitable for evaluating the health benefit derived from the different programme components and those that could help detect possible deficiencies, but emphasized that evaluation should not be concentrated only on certain specific procedures. The aim should be to investigate the entire organization and methods concurrently, because deficiencies may be found in the fusion of the various individual activities.

The health benefit derived from a certain activity may be expressed as an output, such as the number of cases prevented, or the number of patients cured. In order to provide a more meaningful measure it is often advisable to relate this output to a denominator that is well defined in epidemiological terms and directly linked to the principal objective of the programme activity. Thus, the result of case-finding and treatment may be expressed as the number of new patients cured in a certain period of time in relation to the number of new cases estimated to have occurred during the relevant period.

To determine how well the resources have been utilized to achieve certain health benefits it is convenient to relate the benefits to cost. Cost-benefit data can be used directly when comparing alternatives that produce the same type of health benefit, such as different treatment regimens, or different approaches to BCG vaccination. Sometimes, however, certain resources such as manpower, cannot be adequately expressed as a cost. In such instances, the utilization of resources may be studied by other techniques, such as activity sampling, or by setting up test situations under representative local field conditions.

5.4.2 *BCG vaccination*

The Committee discussed the evaluation of BCG vaccination. Although it is impracticable to measure the health benefit directly in terms of the number of cases prevented, it is possible to measure the output of the vaccination service. From controlled trials the efficacy of certain vaccines can be estimated fairly accurately. Moreover, quality control of the vaccine as well as checks on the vaccination technique will give a good indication of how far the efficacy observed in controlled trials is applicable to the field programme. From the efficacy, the coverage, and the risk of disease in the eligible population, the number of cases prevented can be estimated.

Since estimates of the coverage, if based on the number of vaccinations reported, are likely to be very imprecise, it is advisable to obtain an estimate,

by means of a carefully conducted sample survey, of the presence of scars and the distribution of the scar size. Indicators relevant to the quality of vaccination are the proportion of cases of suppurative lymphadenitis (especially in the newborn) and the proportions of abscesses and unsightly scars.

For an accurate assessment of the quality of the vaccine and the vaccination technique, it is necessary to undertake postvaccination tuberculin testing, on a sample basis. However, such tuberculin testing requires special skill.

A general indication of whether the quality and the coverage of BCG vaccination have been adequate in the lower age groups is the incidence of tuberculous meningitis in children. The value of this indicator obviously depends on the availability, utilization, and accuracy of the diagnostic services and the completeness of reporting of this disease.

5.4.3 *Case-finding and treatment*

Case-finding *per se* is not a tuberculosis control measure and any health benefit depends on the ensuing treatment. It is, therefore, appropriate to evaluate case-finding and treatment activities together. On the other hand, if the aim is to pin-point technical and organizational deficiencies, the case-finding and the treatment programmes may be evaluated separately.

As regards case-finding, attention must be paid both to the cases that have been discovered and to those individuals incorrectly diagnosed as having tuberculosis. The benefit of case-finding and therapy cannot, therefore, simply be expressed as a function of the number of cases found and cured. Account must be taken of the accuracy of the diagnostic test procedures (which can be measured by special investigations). Only when this is done can the number of patients who actually benefited from case-finding and treatment (as well as the number that were treated unnecessarily) be estimated.

The Committee laid great emphasis on the overriding importance of regularity in drug-taking throughout the period of treatment. Regularity of drug collection can be estimated from records. Drug ingestion can be measured directly by testing urine specimens from a sample of the patients and this procedure helps detect deficiencies in this vital aspect of the treatment programme.

The inspection of records available in peripheral centres makes it possible to examine certain aspects that are not reflected by the overall results of the case-finding and treatment programme. These records will indicate whether the recommended standard regimens were prescribed, whether the recommended action was taken with respect to defaulters, whether patients have been hospitalized and, if so, for how long and why. In addi-

tion, the proportion of failures, including the proportion of relapses, and the case-fatality rate may lead to the detection of deficiencies in the chain of activities that makes up the case-finding and treatment programme. Other indicators of the quality of the treatment are the proportions of patients with primary, initial, and acquired drug resistance ; these proportions can be measured from time to time.

6. RESEARCH

After reviewing the main trends in tuberculosis research, the Committee considered that it remains important to continue research in a number of directions. It also emphasized the need to test current knowledge under field conditions.

6.1 Epidemiology

Research is still required in the following fields : the pathogenesis of tuberculosis, particularly the occurrence of bacteriologically positive pulmonary tuberculosis following infection, including the estimation of the risk in terms of frequency, time interval, and age, in different socioeconomic conditions ; more appropriate indices for tuberculosis surveillance ; recording, reporting, and the interpretation of data for the purposes of surveillance and programme evaluation ; and the relative frequencies of endogenous reactivation and exogenous reinfection.

The significance of geographical variation in the characteristics of tubercle bacilli should be investigated further. The development of species-specific tuberculins would also be valuable. More attention should be paid to predictive epidemiology, including epidemetric models to improve knowledge of the dynamics of the tuberculosis problem and to provide information for planning and programme strategies.

6.2 Bacteriology and immunology

Further research is required into simplifying and standardizing the direct smear examination and into preserving sputum specimens during transport, decontamination methods, less expensive cultivation methods, and simplified methods for identifying mycobacteria. Immunological methods for identifying tuberculous infection and disease also need further study, as do the factors affecting the intracellular growth of tubercle bacilli.

6.3 Immunization

The Committee was informed of the progress of a large-scale controlled trial of BCG in man, in which the level of protection will be determined

by direct observation in an area where nonspecific tuberculin sensitivity is prevalent. It will take many years before accurate information becomes available, not only on the level of protection, but on its duration, on the dose–response relationship, and on the possible difference in immunogenic capacity between the vaccine strains used in the trial. The Committee strongly recommended that the follow-up of this study should be supported for a minimum of 10 years, after which the position should be reviewed. The worldwide use of BCG vaccination largely precludes the possibility of conducting such a trial in the future.

The Committee considered that proposed new schedules of simultaneous or combined vaccination should be investigated with regard to the likelihood of overloading the immune mechanisms.

The effectiveness and applicability of the bifurcated needle technique needs further investigation.

6.4 Chemotherapy

Research into the duration of the initial intensive phase of chemotherapy and the optimal duration of chemotherapy was recommended. The Committee emphasized the importance of research into short-course regimens, into effective oral intermittent regimens, and into slow-release preparations of isoniazid, because all 3 could lead to substantial improvement in the success of chemotherapy programmes. In relation to the use of slow-release preparations of isoniazid, simpler and more accurate methods of phenotyping rapid and slow inactivators of the drug are required. Drug toxicity and its prevention is an important subject. The Committee emphasized that there remains a need for effective, yet nontoxic, inexpensive new drugs, especially if they prove to be effective in short-course regimens.

Apart from differences in the relapse rate related to the type of disease, other factors influencing the occurrence of relapse have received inadequate attention. In this connexion, research is required into the physiological state of the mycobacteria and the immunological status of the patient.

Improved methods for monitoring the effectiveness of chemotherapy are required, and studies of motivation in relation to regularity of attendance and of taking drugs during ambulatory treatment, including the use of sociological approaches are regarded as a priority.

6.5 The systems analysis approach to tuberculosis control

The Committee recommended more operations research into the decentralization of tuberculosis control measures and their integration at the intermediate and peripheral levels of health services. This research should include assessment of the relative efficiency of bacteriological

examination at peripheral, intermediate, and central laboratories, and the effectiveness of case-finding and treatment activities under different field conditions and at different levels of the health services. In this regard, the use of simple resource allocation models should be considered.

There is also a need for further study of multifactorial analysis methods and of indicators suitable for the planning-programming-budgeting system, as well as of comprehensive methods for evaluating national tuberculosis programmes. The Committee stressed that the measurement of the social consequences of, and economic losses resulting from, tuberculosis (cost–health benefit determinations) deserve more attention.

Finally, further studies are required of methods of health education and public information, particularly with a view to promoting community participation in national tuberculosis programmes.

6.6 Training methods and instructional material

To implement a programme it is essential that it should be accepted by the consumer and be known, understood, and accepted by all grades of staff who are involved in it. All aspects of the programme, even including detailed work instructions, should be described in manuals to be used by all categories of staff.

The training of personnel working at the peripheral level (often termed " front-line workers "), who constitute the majority of the staff operating the programme, must receive particular attention, bearing in mind that their work in tuberculosis control must fit in with their other duties. Training curricula, including well-defined instructional objectives, should be designed taking into account the capabilities of the peripheral workers who will deliver the tuberculosis control measures as part of the minimum " package " health service. To that end, operations research on the best methods of instruction and of learning should be undertaken.

7. ACTIVITIES OF WHO IN THE FIELD OF TUBERCULOSIS

Reviewing the efforts made by WHO during the last decade in promoting the concept of a planned and organized national tuberculosis control programme, the Committee noted that the efforts had met with considerable success in a number of countries where the disease is highly prevalent.

7.1 Training

The Committee noted with satisfaction that an increasing number of key personnel from many countries have received training in modern approaches to tuberculosis control at international courses or at regional

or national seminars. The Committee considered that seminars, particularly at the national level, are indispensable, and suggested that the Organization, if so requested, should assist governments in planning and conducting such meetings.

It also recommended that programme-oriented training of all categories of health worker engaged in tuberculosis control should be intensified. To facilitate this, priority must be given to teacher training.

The Committee recommended that WHO might formulate the outline of a set of standardized and simplified techniques and procedures around which national authorities could elaborate their own health delivery "package". These could be explained in manuals and work instructions covering all the relevant tuberculosis activities. This set of manuals and technical instructions would include the training material required for all types of training institution at the national level. The manuals would also serve as a guide to supervisors during their routine checks of institutions under their technical control and of the performance of peripheral workers. They would provide peripheral workers with all the technical details related to the procedures that they would have to carry out meticulously in their day-to-day work.

7.2 Direct assistance to national tuberculosis programmes

The Committee noted with appreciation the efforts made by WHO to assist countries by providing long-term and short-term technical advice with a variety of objectives, including, for example, measurement of the magnitude of the problem, planning and programming of national tuberculosis control activities, evaluation of control efforts, and advice on improving the quality of nationally produced BCG vaccine.

The Committee also appreciated the continued efforts made by UNICEF to provide countries, on request, with laboratory equipment, standard antituberculosis drugs, and BCG vaccine. It emphasized the importance of an uninterrupted flow of essential supplies (e.g., BCG and standard drugs) for countries dependent on international assistance. Interruption of supplies could doom to failure a nascent national programme and result in the loss of much, or even all of the expenditure and effort hitherto invested. On the other hand, the Committee noted with approval that the policy of providing mobile X-ray units for national tuberculosis programmes has been discontinued.

7.3 Technical information

The Committee expressed its appreciation of the high quality of the technical papers published on tuberculosis in the *Bulletin of the World*

Health Organization and believed that these were of great value to national institutions concerned with tuberculosis control programmes, and to medical schools and high-level health administrators.

7.4 Development of standardized procedures

The Committee noted with satisfaction the considerable progress made in standardizing procedures. As a consequence of WHO research and initiative, the production and quality control of BCG vaccines have become much more uniform. The Committee noted that, in the field of chemotherapy, highly efficient standard regimens have been defined as a result of research, much of which was assisted by WHO.

The Committee recommended that efforts should be continued to simplify and standardize diagnostic methods and treatment.

It is also important to standardize terminology and epidemiological information both for national and international comparison.

7.5 Reference centres

The Committee noted with satisfaction that both international and regional WHO-designated reference centres have fulfilled important functions.

The Committee recommended that the reference system for the control and assay of BCG products should be maintained, and should continue to receive assistance from WHO.

The training facilities in laboratory procedures provided by reference centres for national workers have been useful and should be continued.

There remains a need for reference centres in certain regions to provide facilities for complex examinations, such as the identification of mycobacterial species.

7.6 Research

The Committee reviewed the research activities promoted and coordinated by WHO and recommended that WHO should continue its efforts along the lines followed in recent years. The Committee restated the need for WHO to pursue applied research, particularly in certain fields related to the efficiency of national tuberculosis control programmes.

The Committee recommended that WHO should increase its efforts to coordinate tuberculosis research with research in related fields, such as education and training, development of health services, maternal and child health, managerial sciences, sociology, etc.

The Committee's other proposals on research are set out in section 6.

8. THE ACTIVITIES OF THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND VOLUNTARY ORGANIZATIONS

The Committee's attention was drawn to the current activities of the International Union against Tuberculosis (IUAT) which is a federation of national antituberculosis associations.

The national role of a voluntary antituberculosis association is essentially to complement and support the government tuberculosis control programme. Typical activities include the dissemination of information on tuberculosis and its control, health education campaigns, and the promotion of better communication between the government services and the population. The voluntary organizations should aim to make their services country-wide and to expand them in parallel with the extension of the health services.

Internationally, the role of the IUAT is complementary to that of WHO, and having the flexibility of approach and action of a nongovernmental agency, it can be useful in promoting joint programme activities. The IUAT is currently pursuing research of public health interest under the auspices of its six scientific committees. Special mention may be made of the cooperative studies on chemotherapy, on the chemoprophylaxis of high-risk groups, and of the research into the standardization of bacteriological procedures. The IUAT is also associated with WHO in the field of surveillance, especially in the efforts to obtain epidemiological information of value to governments in deciding their future priorities.

In addition to its publications, the IUAT's periodic conferences and regional seminars provide the major forum for exchange of knowledge on tuberculosis. It is participating in a number of training activities sponsored by WHO, and through its mutual assistance programme is giving support to the work of national associations in developing countries. In particular, it is sponsoring studies of different approaches to the promotion of community participation in health activities.

The IUAT has recently broadened its objectives and now includes chest diseases other than tuberculosis and also community health in its programme. These measures are designed to attract the younger generation of chest specialists and in so doing, maintain their interest in the field of tuberculosis, and also to facilitate the promotion of tuberculosis control programmes in developing countries.

The Committee hoped that close coordination between the official and voluntary tuberculosis agencies would be maintained and intensified.

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